CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-176

CORRESPONDENCE

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

Toll Free: 800-336-7783
Direct Dial: (423)-989-8166
Fax: (423)-989-6113

January 7, 2000

Greg Carrier
Director, Regulatory Affairs

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA ORIG AMENDMENT
N/A

RE: TELEPHONE AMENDMENT - ANDA #75-176
RESPONSE TO CHEMISTRY DEFICIENCIES
Haloperidol Decanoate Injection (50 mg/mL & 100 mg/mL)
1 mL Ampoules and 5 mL Multi-Dose Vials

Dear Mr. Sporn:

Reference is made to King Pharmaceutical's pending ANDA 75-176, Haloperidol Decanoate Injection (50 mg/mL and 100 mg/mL), to the December 22 and December 28, 199 telephone amendments to this application, and to the January 3, 2000 teleconference between Mr. Greg Carrier (King Pharmaceuticals), Mr. David Tengroth (King Pharmaceuticals), Dr. Gill (Chem Team Leader, OGD), Neeru Takira (Review Chemist, OGD) and Ruby Yu (Project Manager, OGD).

As agreed upon in this teleconference, this telephone amendment provides revised specifications for the drug product and drug substance. Revisions to the drug substance specifications consist of establishing a specification for individual unknown impurities of and modification of the limits to reflect those of the current USP 24 (Attachment 1). Revision to the drug product specifications (both release and stability, found in Attachment 2) consist of establishing limits for individual unknown impurities of for release, and for stability (based upon examination of data from the stability batches). Also provided (Attachment 3) as support for the commitment made in the December 28, 199 telephone amendment is a copy of the December 23, 1999 communication from the drug substance manufacturer stating that the impurity

substance.

We feel confident that these revisions constitute a complete response to the concerns presented throughout these discussions. If further clarification is needed, please contact me at (423) 989-8166, or via fax at (423) 989-6113.

Sincerely,
KING PHARMACEUTICALS, INC.

Greg Carrier
Director, Regulatory Affairs

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

Toll Free: 800-336-7783
Direct Dial: (423)-989-8166
Fax: (423)-989-6113

December 28, 1999

Greg Carrier
Director, Regulatory Affairs

ORIG AMENDMENT
N/Am

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: TELEPHONE AMENDMENT - ANDA #75-176
RESPONSE TO CHEMISTRY DEFICIENCIES
Haloperidol Decanoate Injection (50 mg/mL & 100 mg/mL)
1 mL Ampoules and 5 mL Multi-Dose Vials

Dear Mr. Sporn:

Reference is made to King Pharmaceutical's pending ANDA 75-176, Haloperidol Decanoate Injection (50 mg/mL and 100 mg/mL), to the December 13, 1999 teleconference between Mr. Greg Carrier (King Pharmaceuticals) and Dr. Gill (Chem Team Leader, OGD), Neeru Takira (Review Chemist, OGD) and Ruby Yu (Project Manager, OGD) requesting a telephone amendment (chemistry deficiencies) to this application, and the December 22, 1999 telephone amendment provided to 75-176.

This Telephone Amendment supplies additional information in response to the issues presented in the December 13, 1999 telecon and addressed in the December 22, 1999 telephone amendment. This additional information was received from the drug substance manufacturer via fax on December 23, 1999 while King Pharmaceuticals was closed for the holidays.

With regard to OVI testing – the ds manufacturer can't provide a COA showing testing versus USP 24; however, they did provide a certification that methylene chloride is the only analyte included in USP OVI testing that is used in the synthesis of the drug substance haloperidol decanoate. A copy of this letter is attached. Please note that the firm's previous commitment to conduct any necessary testing for OVIs by the methods described in USP 24 or revisions thereof remains unchanged.

Also, based upon information supplied by the ds manufacturer, King Pharmaceuticals certifies that, if tested for such by methods described in USP 24 for haloperidol, the impurity will not be detectable in the drug substance haloperidol decanoate.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 29 1999
OGD

As requested, a copy of this response has been provided via fax, as well as hard copy provided via FedEx overnight delivery.

If any further information is required, please contact me at 423/989-8166, or via fax at 423/989-6113.

Sincerely,
KING PHARMACEUTICALS, INC.

Greg Carrier
Director, Regulatory Affairs

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

Toll Free: 800-336-7783
Direct Dial: (423)-989-8166
Fax: (423)-989-6113

December 22, 1999

Greg Carrier
Director, Regulatory Affairs

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/A

RE: TELEPHONE AMENDMENT
RESPONSE TO CHEMISTRY DEFICIENCIES
ANDA #75-176
Haloperidol Decanoate Injection (50 mg/mL & 100 mg/mL)
1 mL Ampoules and 5 mL Multi-Dose Vials

Dear Mr. Sporn:

Reference is made to King Pharmaceutical's pending ANDA 75-176, Haloperidol Decanoate Injection (50 mg/mL and 100 mg/mL), and to the December 13, 1999 teleconference between Mr. Greg Carrier (King Pharmaceuticals) and Dr. Gill (Chem Team Leader, OGD), Neeru Takira (Review Chemist, OGD) and Ruby Yu (Project Manager, OGD) requesting a telephone amendment (chemistry deficiencies) to this application.

This Telephone Amendment is in response to the issues presented in the December 13, 1999 telecon. For ease of review, each observation is answered in point-by-point fashion. We believe that each issue has been fully addressed.

The firm commits to implementation of the following before manufacture of commercial batches of the subject drug product:

1) Revision of specifications for the drug substance to comply with OVI requirements as described in USP 24 or subsequent revisions thereof. As per the current USP 24, these specifications are as follows:

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

Toll Free: 800-336-7783
Direct Dial: (423)-989-8166
Fax: (423)-989-6113

January 28, 2000

Greg Carrier
Director, Regulatory Affairs

NDA ORIG AMENDMENT
N/A

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: TELEPHONE AMENDMENT - ANDA #75-176
Haloperidol Decanoate Injection (50 mg/mL & 100 mg/mL)
1 mL Ampoules and 5 mL Multi-Dose Vials

Dear Mr. Sporn:

Reference is made to King Pharmaceutical's pending ANDA 75-176, Haloperidol Decanoate Injection (50 mg/mL and 100 mg/mL), and to the January 28, 2000 teleconference between Greg Carrier (King Pharmaceuticals) and Ruby Yu (Project Manager, OGD).

As requested, the firm agrees that the referenced drug product will meet the requirements of USP<1> throughout the expiration dating period, as evidenced by the results of the testing program conducted per the stability protocol within this application.

If further clarification is needed, please contact me at (423)989-8166, or via fax at (423)989-6113.

Sincerely,
KING PHARMACEUTICALS, INC.

Greg Carrier
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 31 2000
OGD

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

Toll Free: 800-336-7783
Direct Dial: (423)-989-8166
Fax: (423)-989-6113

November 18, 1999

Greg Carrier
Director, Regulatory Affairs

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: TELEPHONE AMENDMENT
ANDA #75-176
Haloperidol Decanoate Injection (50 mg/mL & 100 mg/mL)

Dear Mr. Sporn:

Reference is made to King Pharmaceutical's pending ANDA 75-176, Haloperidol Decanoate Injection (50 mg/mL and 100 mg/mL). Reference is also made to the telephone conversation of November 18, 1999 between Andrea High, FDA/OGD and Greg Carrier, King Pharmaceuticals, in which Ms. High requested certain microbiology information be supplied in a telephone amendment to this application.

This Telephone Amendment is submitted to provide revised maximum valid dilution (MVD) calculations for the endotoxin testing of the finished drug product. In light of the information supplied by FDA indicating that the endotoxin limits presented in the 1987 LAL testing guidance may not be applicable due to labeling changes affecting maximum dosing, the firm has recalculated the MVD and the corresponding release and stability specification for each of the product concentrations, as presented below:

MVC =

For a maximum human dose of 450mg haloperidol decanoate (per 70 kg adult) delivered

Therefore,

The firm expresses release and stability specifications as " ". The MVD values translate to specifications as follows:

Therefore, the release and stability specifications for each strength are:

As agreed upon in the November 18, 1999 telephone conversation, the firm commits to modify the release and stability specifications (including the MDV values therein) prior to manufacture and testing of commercial drug product to match those indicated above.

If any further information is required, please contact me at 423/989-8166, or via fax at 423/989-6113.

Sincerely,
KING PHARMACEUTICALS, INC.

Greg Carrier
Director, Regulatory Affairs

Microbiology Comments to be Provided to the Applicant

ANDA: 75-176 APPLICANT: King Pharmaceuticals

DRUG PRODUCT: Haloperidol Decanoate Injection , 50 mg/mL and 100 mg/mL in 1 mL Ampules and 5 mL Multi-dose Vials

Microbiology Deficiencies:

1. You provided which states that the positive control should exhibit growth. units exhibited growth. You did not consider the lack of growth in a breached positive control. Please clarify this point.

2. Regarding endotoxin limits:

   a. You stated that the subject drug product was not in the current (USP XXIII) and referred to the 1992 Guideline for Validation of Limulus Amebocyte Lysate Test as an End-Product Test for Human and Animal Parenteral Drugs, Biological Products and Medical Devices. The limit of 71.4 EU/mg is listed in the USP for Haloperidol Injection and is the same limit listed in the 1992 FDA Guideline draft and the 1987 FDA Guideline. The maximum valid dilution should be based on the maximum dose that can be administered. You should provide your calculations as the description in your response was not clear.

   b. You should note that the official FDA guideline is the 1987 version and not the 1992 draft. You should also note that the guideline [or draft] may not contain accurate endotoxin limits for this or any drug products because labeling changes that would effect the administration of a drug product may not be reflected after the guideline [or draft] date.

Please clearly identify your amendment as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

Mary Fanning, M.D., Ph.D.
Associate Director for Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

Toll Free: 800-336-7783
Direct Dial: (423)-989-8166
Fax: (423)-989-6113

August 27, 1999

Greg Carrier
Director, Regulatory Affairs

ORIG AMENDMENT
N/A

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: MINOR AMENDMENT
RESPONSE TO CHEMISTRY AND MICROBIOLOGY DEFICIENCIES
ANDA #75-176
Haloperidol Decanoate Injection (50 mg/mL & 100 mg/mL)
1 mL Ampules and 5 mL Multi-Dose Vials

Dear Mr. Sporn:

Reference is made to King Pharmaceutical's pending ANDA 75-176, Haloperidol Decanoate Injection (50 mg/mL and 100 mg/mL), and to FDA's fax transmission of July 22, 1999 requesting a minor amendment (chemistry and microbiology deficiencies) to this application.

This Minor Amendment is in response to the issues presented in the July 22, 1999 letter. For ease of review, each observation is answered in point-by-point fashion. We believe that each issue has been fully addressed.

This Amendment is being submitted in duplicate as archival copies in blue binders and as review copies in red binders. By signature of this letter, it is certified that a complete and true copy of this Minor Amendment to the ANDA is being forwarded to the FDA Nashville District Office concurrently with submission to OGD. Inquiries concerning this application may be directed to my attention at the above listed address. I can be reached by telephone directly at 423-989-8166 or via fax at 423-989-6113.

Sincerely,
KING PHARMACEUTICALS, INC.

Greg Carrier
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 30 1999
OGD

JUL 22 1999

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA 75-176 **APPLICANT:** King Pharmaceuticals, Inc.

DRUG PRODUCT: Haloperidol Decanoate Injection, 50 mg/mL and 100 mg/mL, 1 mL Ampules and 5 mL Vials

The deficiency presented below represent FACSIMILE deficiency.

A. Deficiency:

1. Please reduce the limits for individual (known and unknown) impurities to levels that are closer to the observed values in the stability test report.

2. Please refer to the attached microbiology deficiencies.

B. In addition to responding to the deficiency presented above, please note and acknowledge the following comments in your response:

1. Methods validation for drug substance and drug product has been requested from the FDA district laboratory. Please submit samples promptly when requested.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Microbiology Comments to be Provided to the Applicant

ANDA: 75-176 APPLICANT: King Pharmaceuticals

DRUG PRODUCT: Haloperidol Decanoate Injection,
50 mg/mL and 100 mg/mL

A. Microbiology Deficiencies:

1. Regarding the container/closure integrity test for vials, the description of the positive control appears to be a "growth promotion" test and not a test of the closure. Please provide a closure integrity test with an appropriate positive control.

2. The APET determines if the preservative [at specified concentration levels] is effective as an antimicrobial agent. You should consider performing the APET at the minimum label claim.

3. You have listed the endotoxin limit of for the 50 mg/mL strength and for the 100 mg/mL strength for the subject drug product(s). Please explain how this endotoxin limit was established and provide the validation of the bacterial endotoxin test, including the maximum valid dilution.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The subject drug product is based and overlaid with . These conditions may favor anaerobic bacteria.

2. Regarding the 14-day hold validation reference for water for injection, WFI used for parenteral products should be tested daily regardless of validated of "holding times".

Please clearly identify your amendment as "RESPONSE TO

MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

Mary Fanning

Mary Fanning, M.D., Ph.D.
Associate Director for Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

:rmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

Toll Free: 800-336-7783
Direct Dial: (423)-989-8166
Fax: (423)-989-6113

May 19, 1999

Greg Carrier
Director, Regulatory Affairs

NEW CORRESP
NC
FAX

VIA FEDERAL EXPRESS

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: FACSIMILE AMENDMENT - ANDA #75-176;
Haloperidol Decanoate Injection (50 mg/mL & 100 mg/mL)
1 mL Ampules and 5 mL Multi-Dose Vials

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application (ANDA) for Haloperidol Decanoate Injection, 50 mg/mL and 100 mg/mL (1 mL ampules and 5 mL multi-dose vials) submitted to the Agency by King Pharmaceuticals on July 30, 1997, under Section 505 (j) of the Federal Food, Drug and Cosmetic Act. Reference is also made to the Major Amendment to this ANDA dated November 23, 1998, and a Facsimile Amendment letter from FDA dated May 3, 1999.

This facsimile amendment is intended to respond to the issues raised in the May 3, 1999 letter. Each deficiency is addressed in a point-by-point manner; for ease of review, the observations are reproduced herein as italic text, followed by the response. We believe that this facsimile amendment satisfactorily all of the listed deficiencies.

If further information is needed, I can be contacted at 423/989-8166 or via fax at 423-989-6113.

Yours truly,

KING PHARMACEUTICALS, INC.

Greg Carrier
Director, Regulatory Affairs

MAY - 3 1999

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-176 **APPLICANT:** King Pharmaceuticals, Inc.

DRUG PRODUCT: Haloperidol Decanoate Injection, 50 mg/mL and 100 mg/mL, 1 mL Ampules and 5 mL Vials

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1. Bacterial endotoxin specifications listed on the COA's for both strengths of the drug product and room temperature stability data are different from the quality assurance standards and procedures. Please correct.

2. Specification of color for both strengths of the drug product and stability samples is very high. Please provide the actual test results and tighten specifications.

3. Please include other requirements in your drug product release controls to meet the USP 23 requirements under injections <1>.

4. Container size listed on the COA's for drug product batch PLT-290 and PLT-292 are incorrect. Please correct and provide the revised COA's.

5. Please revise the stability specifications for both strengths (50 and 100 mg/mL) to include the limits for particulate matter and volume in container.

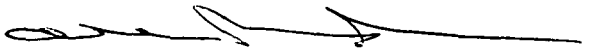
6. Please tighten the stability specification of impurities/ degradants (individual known, unknown, and total) for both strengths based on your test data.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The microbiological section of your application is pending review. Comments, if any, will be communicated at a later date.

2. Method validation for drug substance and drug product have been requested from the FDA district laboratory. Please submit samples promptly when requested.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Microbiology Comments to be Provided to the Applicant

ANDA: 75-176 APPLICANT: King Pharmaceuticals

DRUG PRODUCT: Haloperidol Decanoate Injection, 50 mg/mL and 100 mg/mL

A. Microbiology Deficiencies:

1. Regarding the container/closure integrity test for vials, the description of the positive control appears to be a "growth promotion" test and not a test of the closure. Please provide a closure integrity test with an appropriate positive control.

2. The APET determines if the preservative [at specified concentration levels] is effective as an antimicrobial agent. You should consider performing the APET at the minimum label claim.

3. You have listed the endotoxin limit of ., for the 50 mg/mL strength and for the 100 mg/mL strength for the subject drug product(s). Please explain how this endotoxin limit was established and provide the validation of the bacterial endotoxin test, including the maximum valid dilution.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The subject drug product is and overlaid with These conditions may favor anaerobic bacteria.

2. Regarding the 14-day hold validation reference for water for injection, WFI used for parenteral products should be tested daily regardless of validated of "holding times".

Please clearly identify your amendment as "RESPONSE TO

MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

Mary Fanning, M.D., Ph.D.
Associate Director for Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-423-989-8001
Fax: 1-423-989-6113

November 23, 1998

Thomas K. Rogers, III, M.S.
Vice President, Regulatory Affairs

VIA FEDERAL EXPRESS

NDA ORIG AMENDMENT
N/AC

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: MAJOR AMENDMENT - ANDA #75-176;
Haloperidol Decanoate Injection (50 mg/mL & 100 mg/mL)
1 mL Ampules and 5 mL Multi-Dose Vials

Dear Mr. Sporn:

An Abbreviated New Drug Application (ANDA) for Haloperidol Decanoate Injection, 50 mg/mL and 100 mg/mL (1 mL ampules and 5 mL multi-dose vials) was submitted to the Agency by King Pharmaceuticals on July 30, 1997, under Section 505 (j) of the Federal Food, Drug and Cosmetic Act. A "Not Approvable" letter was issued by the Agency on December 22, 1997. A Microbiology review deficiency letter was later issued by the Agency on June 15, 1998.

This **Major Amendment** is provided in two volumes. The information presented in Volume 1 is intended to respond to all objections cited in the December 22, 1997 and June 15, 1998 letters. To facilitate the review process, each deficiency noted in the letter has been addressed in point-by-point fashion. We believe that all of the objections have been satisfactorily addressed.

Volume 2 is provided in support of a to be used for the and of the vials and ampuls for this drug product. The oven previously used and submitted in the original application has been replaced with a . The information package presented within Volume 2 has been previously submitted to the Agency for review under the following approved applications:

Each submission is identical with exception of the inclusion of product-specific master batch records reflecting the parameters required by the

RECEIVED
RECEIVED
NOV 24 1998

This Amendment is being submitted in duplicate as archival copies in blue binders and as review copies in red binders. By signature of this letter, it is certified that a complete and true copy of this Major Amendment to the ANDA is being forwarded to the FDA Nashville District Office concurrently with the submission of the application to OGD. Inquiries concerning this application may be directed to my attention at the above listed address. I can be reached by telephone directly at 423-989-8172 or via fax at 423-989-6113.

Yours truly,

KING PHARMACEUTICALS, INC.

Thomas K. Rogers, III
Vice-President, Regulatory Affairs

Enclosures

Microbiology Comments to be Provided to the Applicant

ANDA: 75-176 APPLICANT: King Pharmaceuticals

DRUG PRODUCT: Haloperidol Decanoate Injection, 50 mg/mL and 100 mg/mL, in 1 mL Ampuls and 5 mL Multiple Dose Vials

A. Microbiology Deficiencies:

1. Regarding , you should specify in the batch record the minimum acceptable bubble point for integrity testing of the Please note if the bubble points used are product-specific.

2. Regarding the process simulation summaries:

   a. You should consider describing the "damaged" containers in the media fill reports, i.e., it appeared from the reports provided that the minimum units required for a media fill was not met.

   b. You should explain why units are the minimum fill amount in Vol. 1.2, p. 521 and units is desribed in Vol. 1.2, p. 275.

3. Regarding environmental monitoring:

   a. Please comment on whether the tests include molds, yeasts and anaerobes, etc.

   b. Please explain why and where the plates are kept after the

   c. You did not make a specific statement regarding the disposition of product before or after the discovery of excursions, during investigations, failed media fills, etc.

   d. You noted fingertips and masks as testing sites for filling personnel but did not indicate if the gown was tested, i.e., sleeves, chest, etc....

   e. Please specify the microbial and endotoxin limits for WFI and the frequency of point(s)-of-use testing.

f. You should provide the results of the bioburden samples for the subject drug product as they do not appear to be noted in the batch records.

g. The batch records indicate a problem with . Please explain why there did not appear to be a deviation/investigation report associated with the incident(s).

4. Regarding container/closure integrity:

a. You referred to for growth promotion procedures that did not appear to be provided. vials were taken from a media fill for testing. vials were used as samples, 1 vial was used as a negative control. Please explain the positive controls and the disposition of the remaining vials.

b. Please provide a validation summary for the leak test for the ampuls.

c. Please provide a statement regarding the acceptance of leaking vials.

5. Please provide evidence that the APETs provided in the application were tested to 85% of the preservative as the label claims (Vol. 1.3, p. 703).

6. Regarding release and the stability protocol, you did not include endotoxin testing for the injectable subject drug product.

7. Please clarify whether the commitment to place one lot on stability for each container configuration included each strength of the subject drug product.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. You may want to consider confirming the value for the .

2. Regarding media fills, the industry standard has been to accept up to 0.1% contamination rate for a media fill; however, with current methods, the contamination rate should be closer to "0" and the contamination rate should not increase with larger batch sizes.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

DEC 22 1997

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-176 **APPLICANT:** King Pharmaceuticals, Inc.

DRUG PRODUCT: Haloperidol Decanoate Injection, 50 mg/mL and 100 mg/mL, 1 mL Ampules and 5 mL Vials

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

Raw material controls - active and inactive ingredients:

Certificate of Analysis (COA) drug substance:

1. Organic volatile impurities testing (USP 23 <467>) has not been provided on the manufacturer's COA for the drug substance. Please provide the testing data or a statement from the manufacturer to ensure that none of the OVIs is used in the manufacture of drug substance.

2. The IR spectra on page 107 standard for comparison with haloperidol) does not match with IR spectra on page 108 (haloperidol decanoate 910909 C#33463). Please explain.

3. On page 103, you have used an in-house standard for identification testing. Please explain how you qualify your in-house standard.

4. Please perform testing, set limits and specifications for degradants, individual and total impurities, and residual solvents) for the drug substance and provide them on the COA.

5. Heavy metals specification has not been provided on the manufacturer's COA. Please perform the testing, set the limits and provide the specification on the COA.

Inactives:

6. Please provide your COA for ith manufacture's lot 42876, and your control no. 33713, tested/released on 7/3/96.

7. Please revise your specifications on page 128 for halogenated compounds and halide from passes test to not more than 0.03% as Cl according to USP 23/NF 18 monograph and provide them on the COA.

8. On page 128, you have reported N/A for outside testing. However Section X, page 155, indicates has been tested for OVIs by . Please clarify.

9. Please provide your COA for Sesame Oil NF, with manufacture's lot 42814, and your control no. 33345, tested/released on 5/31/96.

10. On page 132, you have indicated * (test not in sop for this product) for fatty acids (COA). According to USP 23/NF 18, the solidification range of fatty acids is one test. Please correct it.

11. a. Your specification and limits for the saponification value test in sesame oil do not agree with USP 23/NF 18 (page 121 and 132). Please correct.

    b. The test results for saponification value (COA) on page 132 and assay on page 133 do not meet USP 23/NF 18 specifications. Please check your methodology.

12. Please provide the COA which includes carbon monoxide, oxygen, and assay testing from for Nitrogen NF.

13. Please provide the identification test results for dimethicone to meet USP 23/NF 18 specifications on the manufacture's COA.

14. Please provide a commitment from the manufacturer of dimethicone that the identification testing will be performed on every lot manufactured to qualify the material.

15. On page 150, the manufacturer's COA (lot HH035356) for dimethicone shows the review date of 5/5/95. Whereas on page 151, your QA raw material report (control no. 31844) shows that the material was received on 4/18/95 and tested and released on 5/4/95. Please explain.

16. Please provide your retesting schedule for the drug substance.

17. Please revise your retesting schedule for inactive ingredients. The testing for the inactives should include a minimum of an identification and assay in addition to microbial testing where appropriate.

Laboratory Controls - In-process, Finished Drug Product:

18. Please provide the COA from , Inc. for drug product preservative effectiveness testing.

Minor Review of All comments endotoxin testing. 6/6/96 See QA audit in the Division file.

Drug product controls:

19. a. Please provide information for the qualification of your reference standard used in the method validation by

    b. Please include an APHA test for monitoring the color. Establish and provide the release specification for the drug product.

    c. Please include specifications for particulate matter.

    d. Please establish the limits and specifications for impurities/degradents (individual and total) in the drug product. Tests and specifications for the degradent should be established.

    e. Please provide the revised COA for the exhibit batches including the recommendations made in comments b-d above. In addition, please provide your revised release specifications for the drug product.

20. You have provided comparative data generated by your QA Lab on page 843 for first two shipments (control no. 33463 and 33464). Please provide comparative data for the third shipment of haloperidol decanoate for raw material qualification.

21. Comparison of sample and impurities chromatograms on page 861 and 862 show that haloperidol nonanoate peak (RT 12.76 minutes) might be interfering with analyte haloperidol decanoate peak (RT 13.06 minutes). Please clarify.

22. Please provide the information for the purity of the haloperidol decanoate (analyte) peak.

Stability:

23. Your specifications for sterility in quality assurance's stability test procedures provided on pages 927-938 are different from the stability protocol included on pages 923-926. Please correct them.

24. Please establish the limits and specifications for haloperidol and peaks eluting after haloperidol decanoate and include them in quality assurance's stability test procedures for release of finished product and stability testing. Tests and specifications for the degradent should be established.

25. Please include the limits and specifications for benzyl alcohol in stability procedures, pages 927 and 933.

26. Please include the orientation of samples in your post approval stability protocol.

27. Please explain why the assay value of peaks eluting after the analyte peak (haloperidol decanoate) are increasing with time in your stability report for the exhibit batches.

28. Please revise your stability specifications to include color in APHA units, impurities/degradents (individual and total).

29. Please provide accelerated stability data at 40°C ± 2°C/75% ± 5% RH. Also, provide all available stability data.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your bioequivalence waiver request is under review. After this review is completed, any deficiencies found will be communicated to you under a separate cover.

2. The microbiological section of your application is under review. Review comments, if any, will be communicated separately.

3. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with CGMP at the time of approval.

4. Upon the resolution of the deficiencies of the method validation indicated above, the analytical methods will need to be validated by the FDA laboratory.

Sincerely yours,

/S/ 12/16/97

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-176 APPLICANT:King Pharmaceuticals, Inc.

DRUG PRODUCT: Haloperidol Decanoate Injection 50mg/ml in 1 ml and 5 ml vials, 100 mg/ml in 1 ml and 5 ml vials.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-423-989-8001
Fax 1-423-989-6113

Thomas K. Rogers, III
Director, Regulatory Affairs

July 30, 1997

505(j)(1) OK 8/21/97 Gregory S. Davis

VIA FEDERAL EXPRESS

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Document Control Room
U.S. FOOD & DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: **Original ANDA Submission**
Haloperidol Decanoate 50 - 1 mL Ampule and 5 mL Multiple Dose Vial
(50 mg haloperidol present as 70.5 mg per mL haloperidol decanoate)
Haloperidol Decanoate 100 - 1 mL Ampule and 5 mL Multiple Dose Vial
(100 mg haloperidol present as 141.05 mg per mL haloperidol decanoate)

Dear Mr. Sporn:

King Pharmaceuticals, Inc. is submitting herewith an original Abbreviated New Drug Application (ANDA) seeking approval to market Haloperidol Decanoate 50 (Haloperidol Decanoate Injection 50 mg/mL - 1 mL ampule and 5 mL multiple dose vial) and Haloperidol Decanoate 100 (Haloperidol Decanoate Injection 100 mg/mL - 1 mL ampule and 5 mL multiple dose vial). This ANDA is based upon the reference listed products Haldol® Decanoate 50 and Haldol® Decanoate 100 that are manufactured by McNeil Pharmaceutical. Haldol® Decanoate 50 and Haldol® Decanoate 100 are approved under the New Drug Application # 18-701.

This application consists of three volumes. An archival copy is being filed in blue folders and a technical review copy is being filed in red folders. A separate copy of the bioequivalence section is being submitted in an orange folder. Since this application seeks approval of a sterile injectable product, a Sterile Process Validation Package is included within Section XI of the ANDA. Two additional copies of the analytical methods validation section are provided in black folders. For more detailed information on the organization of this application, please refer to the "Executive Summary" which is included immediately following the Table of Contents.

By this letter, it is further certified that a true copy of the technical sections of the application (including a copy of FDA application form 356h and a certification that the contents are a true copy of the application filed with the Office of Generic Drugs) was sent to the Nashville District office of the FDA. This "field copy" was contained in burgundy folders.

Please direct any communications regarding this submission to my attention at the above address, or I may be reached by telephone at 423/989-8172 or via FAX at 423/989-6113. Thank you for your prompt attention to this application.

Yours truly,

KING PHARMACEUTICALS, INC.

Thomas K. Rogers III
Senior Director, Regulatory Affairs

ANDA 75-176

King Pharmaceuticals, Inc.
Attention: Thomas K. Rogers, III
501 Fifth Street
Bristol TN 37620

SEP 3 1997

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Haloperidol Decanoate Injection, 50 mg/ml and 100 mg/ml, 1 ml ampules and 5 ml vials

DATE OF APPLICATION: July 30, 1997

DATE OF RECEIPT: July 31, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Joseph Buccine
Project Manager
(301) 827-5848

Sincerely yours,

9/3/97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-176 APPLICANT:King Pharmaceuticals, Inc.

DRUG PRODUCT: Haloperidol Decanoate Injection 50mg/ml in 1 ml and 5 ml vials, 100 mg/ml in 1 ml and 5 ml vials.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research